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Hypercapnia-induced increases in cerebral blood flow do not improve lower body negative pressure tolerance during hyperthermia.

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Running title: Effects of hypercapnia during a hyperthermic hypotensive challenge

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Abstract

Heat-related decreases in cerebral perfusion are partly the result of ventilatory related reductions in arterial carbon dioxide (CO_2) tension. Cerebral perfusion likely contributes to an individual's tolerance to a challenge like lower body negative pressure (LBNP). Thus, increasing cerebral perfusion may prolong LBNP tolerance. This study tested the hypothesis that a hypercapnia-induced increase in cerebral perfusion improves LBNP tolerance in hyperthermic individuals**.** Eleven individuals (31 ±7 y; 75 ±12 kg) underwent passive heat stress (increased intestinal temperature ~1.5°C) followed by a progressive LBNP challenge to tolerance on two separate days (randomized). From 30 mm Hg LBNP, subjects inhaled either (blinded) a hypercapnic gas mixture (5% CO_2, 21% oxygen, balanced nitrogen) or room air (SHAM). LBNP tolerance was quantified via the cumulative stress index (CSI). Mean middle cerebral artery blood velocity ($MCAv_{mean}$,) and end-tidal CO_2 ($P_{ET}CO_2$,) were also measured. 5% CO_2 inhalation increased $P_{ET}CO_2$ at ~40 mm Hg LBNP (by 16 ±4 mmHg) and at LBNP tolerance (by 18 ±5 mmHg), compared to SHAM ($P<0.01$). Subsequently, $MCAv_{mean}$ was higher in the 5% CO_2 trial during ~40 mm Hg LBNP (by 21 ±12 $cm.s^{-1}$, ~31%) and at LBNP tolerance (by 18 ±10 $cm.s^{-1}$, ~25%) relative to the SHAM ($P<0.01$). However, hypercapnia-induced increases in $MCAv_{mean}$ did not alter LBNP tolerance (5% CO_2 CSI: 339 ±155 mm Hg x min; SHAM CSI: 273 ±158 mm Hg x min; $P=0.26$). These data indicate that inhaling a hypercapnic gas mixture increases cerebral perfusion during LBNP but does not improve LBNP tolerance when hyperthermic.

Keywords: hypercapnia, heat stress, LBNP

Introduction

Heat-induced hyperventilation in humans (14, 16) is associated with high skin *and* body core temperatures (T_c in excess of +1.0°C) (6, 12, 17). In normothermic humans, hyperventilation can also occur during a hypotensive challenge, such as lower body negative pressure (LBNP) or head-up tilt (30). During a combined hyperthermic *and* hypotensive challenge there is a marked increase in ventilation that significantly reduces end-tidal and arterial carbon dioxide tensions (5, 31).

Cerebral perfusion is profoundly influenced by arterial carbon dioxide tension (3, 19), changing 2-5% per mm Hg of carbon dioxide (32). Increases and decreases in arterial carbon dioxide tension influence cerebral perfusion via cerebral arteriolar vasodilation and vasoconstriction, respectively (1). Subsequently, hyperventilation and related reductions in arterial carbon dioxide tension significantly reduce cerebral perfusion. During steady-state head-up tilt, cerebral hypoperfusion can be reversed via CO_2 rebreathing, which elevates arterial carbon dioxide tension (30). Furthermore, inhaling a 5% CO_2 gas mixture prevents hypocapnia and improves LBNP tolerance under normothermic conditions, presumably due to increases in cerebral perfusion (18). However, an index of cerebral perfusion was not measured in that study, and thus it remains unknown how cerebral perfusion responded to the hypercapnic stimulus at LBNP tolerance.

Heat stress significantly reduces an individual's ability to withstand a hypotensive challenge (21, 28). While the mechanisms underlying this impaired tolerance are not fully elucidated, it is clear that hyperthermia reduces cerebral perfusion at rest (4, 10, 29, 40) and that these reductions are exacerbated during a hypotensive perturbation (i.e., tilt or stand) (25, 40). Hyperventilation and related reductions in $P_{ET}CO_2$ are purported to contribute to at least 50% of said reductions in cerebral perfusion (4, 11, 29, 33). As such, inhaling a hypercapnic gas mixture and elevating cerebral perfusion should improve tolerance to a hypotensive challenge, given that cerebral hypoperfusion ultimately results in syncope (38). However, it is unknown if inhaling a hypercapnic gas mixture and elevating cerebral perfusion improves tolerance

to a hypotensive challenge during heat stress. Such information could have important ramifications in the treatment of hemorrhagic, hyperthermic individuals, as it may extend treatment time. Therefore, the purpose of this study was to test the hypothesis that a hypercapnia-induced increase in cerebral perfusion improves LBNP tolerance in hyperthermic individuals**.**

Methods

Participants

Eleven healthy individuals (8 males, 3 females; 31 ±7 y, 75 ±12 kg, body mass index, 25 ±3 $kg.m^2$) participated in this study. Subjects were not taking medications and were free of any known cardiovascular, metabolic or neurological diseases and were non-smokers. Repeated testing was conducted at the same phase of each female subject's menstrual cycle, although menstrual cycle phase was not controlled for between subjects as tolerance to a hyperthermic hypotensive challenge is unaffected by menstrual cycle phase (28). Subjects abstained from exercise and alcohol for 24 h prior, as well as caffeine for 12 h prior to testing. Written informed consent was obtained before participation in this study, which was approved by the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas. All procedures conformed to the standards set by the *Declaration of Helsinki*.

Instrumentation

At the beginning of each experimental day, subjects voided their bladder before nude body mass was recorded. Urine specific gravity was measured using a digital refractometer. Subjects were then dressed in a long-sleeved and legged, two-pieced, tube-lined perfusion suit (Med-Eng, Ottawa, Canada) enabling the control of skin temperature and T_c via the temperature of the water perfusing the suit. Body core temperature was measured using a telemetry temperature pill swallowed ~2 h before the onset of data collection (HQ Inc., Palmetto, FL, USA). Whole-body mean skin temperature (Tsk) was measured from the electrical average of six thermocouples (37)

fixed to the skin with porous adhesive tape. Beat-to-beat arterial blood pressure was measured and reconstructed to the brachial artery via finger cuff photoplethysmography (Finometer Pro, FMS, Amsterdam, the Netherlands or NexFin HD, BMEYE B.V, Amsterdam, Netherlands). Arterial blood pressure was also measured by auscultation of the brachial artery (Tango, Suntech Medical Instruments, Raleigh, NC, USA). Finger arterial pressure was used for data analysis while measures from the brachial artery and Finometer were used to aid the detection of ensuing syncope. Mean blood velocity in the right middle cerebral artery ($MCAv_{mean}$) served as an index of cerebral perfusion and was measured using 2 MHz pulsed Doppler ultrasound (Multiflow, DWL Elektronische Systeme, Singen, Germany). The Doppler probe was maintained in position using a commercially available headpiece. An index of cerebrovascular conductance (CBVC) was calculated as $MCAv_{mean}$/mean arterial pressure (MAP). Expired air was sampled via a facemask attached to a two-way valve (Hans Rudolf, inc. Shawnee, KS, USA). Ventilatory parameters (ventilation, tidal volume, breathing rate) were measured (in BTPS) using an automated gas analysis system (TrueOne 2400, Parvo-Medics, Provo, UT, USA), with values recorded over 15-s epochs. The partial pressure of $P_{ET}CO_2$ was sampled from the mask and measured using a capnograph (9004 Capnocheck® Plus, Smiths Medical International Ltd, Watford, Herts, UK). Heart rate was collected from an electrocardiogram signal (Agilent, Munich, Germany) interfaced with a cardiotachometer (1000 Hz sampling rate, CWE, Ardmore, PA, USA). Thermal and hemodynamic data were acquired continuously at 50 Hz throughout the experiment (Biopac, Santa Barbara, CA, USA).

Experimental protocol

Subjects reported to the laboratory on two separate occasions. At each visit subjects underwent passive heat stress followed by LBNP to tolerance. Experimental trials were at least 3 days apart and were performed at the same time of day. Following instrumentation, subjects were positioned in the LBNP box that was sealed at the level of the iliac crest. Subjects rested quietly while normothermic water (34°C) circulated

through the suit for at least 30 min. After ~20 min of wearing a face mask connected to the gas analysis system (ensuring steady-state ventilatory responses), normothermic baseline thermal, hemodynamic and respiratory measures were obtained for 6 min while the subject breathed room air. Subjects were then passively heated by circulating ~49°C water through the suit until T_c increased by ~1.3°C, at which point water temperature was lowered to ~46°C. The face mask was reattached 5-10 min before Pre-LBNP measures were obtained. Progressive LBNP to tolerance was initiated after T_c was raised ~1.5°C. Beginning at 20 mm Hg, 3 min stages of LBNP were applied at 10 mm Hg per stage until the occurrence of syncopal symptoms. In both trials, subjects inhaled room air during the 20 mm Hg LBNP stage. In the CO_2 trial, subjects inhaled a hypercapnic gas mixture (5% CO_2, 21% oxygen, balanced nitrogen) from the onset of the 30 mm Hg stage through to LBNP tolerance. In the SHAM trial, subjects continued to breathe room air. Subjects were blinded to the gas mixture they were inhaling, which was administered in a randomized and counterbalance manner between trials. Criteria for LBNP test termination were: continued self reporting by the subject of feeling faint and/or sustained nausea; a rapid and progressive decrease in blood pressure resulting in sustained systolic blood pressure being less than 80 mm Hg; and/or relative bradycardia accompanied by narrowing of pulse pressure. Typically, a combination of the aforementioned conditions was observed at the cessation of the tolerance test. The total time of each test was measured and used to determine a cumulative stress index (CSI), which was calculated by summing the product of the negative pressure and the duration at that negative pressure (e.g., 20 mm Hg x 3 min + 30 mmHg × 3 min + 40 mmHg ×3 min, etc.) until test termination (23, 27).

Data Analysis

In both the SHAM and CO_2 trials, 60 s of data were averaged for normothermic baseline measures. Pre-LBNP heat stress values were averaged from 60 s of data prior to the onset of LBNP. During LBNP, data from the last 60 s at 20 mm Hg and the highest common LBNP stage completed by each respective participant in both trials (classified

as 'severe') were analysed. Hemodynamic LBNP tolerance data were obtained by averaging responses during the last 10 s prior to cessation of the LBNP challenge due to syncopal symptoms (26). Ventilatory LBNP tolerance data were obtained by averaging responses during the last 30 s, thus allowing for inclusion of multiple breaths in this analysis.

A two-way repeated measures analysis of variance (ANOVA) with main factors of Time (normothermia, heat stress, 20 mm Hg LBNP, severe LBNP, LBNP tolerance) and experimental day (SHAM vs. CO_2) was used to identify differences in thermal, hemodynamic and respiratory measures between the SHAM and CO_2 trials. Bonferroni-corrected post-hoc tests were used to determine differences when a significant interaction was identified from the ANOVA. Paired t-tests were used to identify differences in CSI, body mass and urine specific gravity. The *a priori* α level for all analyses was set at 0.05. Results are reported as the mean ±S.D.

Results

Prior to instrumentation, subjects' body mass (SHAM, 74.8 ±12.4 kg vs. CO_2, 74.5 ±12.5 kg; P =0.15) and urine specific gravity (SHAM, 1.014 ±0.006 vs. CO_2, 1.011 ±0.005; P =0.39) were similar between experimental days. Thermal, hemodynamic and respiratory baseline measures, while subjects were normothermic, were not different between the two experimental trials (P >0.05, Table 1). Prior to the onset of LBNP, passive heat stress caused similar (P >0.05) increases in T_c (~1.3°C) and Tsk (~3.9°C), as well as similar hemodynamic and respiratory responses (P>0.05; see Table 1). At the completion of testing, sweating-induced reductions in body mass were similar (P =0.79) in both the SHAM and CO_2 trials (-1.2 ±0.5 and -1.1 ±0.4 kg, respectively).

LBNP tolerance was similar (P = 0.26) between the two trials, with no difference in CSI (SHAM: 273 ±158 mm Hg x min vs. CO_2: 339 ±155 mm Hg x min, P =0.26), time to tolerance (SHAM: 514 ±211 s vs. CO_2: 604 ±199 s, P = 0.22) or the final LBNP stage reached (SHAM: 50 ±10 vs. CO_2: 50 ±10 mm Hg, P = 0.37). At 20 mm Hg LBNP, respiratory and hemodynamic variables were not different between trials (Figures 1, 2 &

3). Under severe LBNP (~40 mm Hg LBNP), inhaling hypercapnic gas increased $P_{ET}CO_2$ (by 16 ±4 mm Hg, P <0.01), ventilation (by 5.2 ±8.2 L.min^{-1}, P =0.03), $MCAv_{mean}$ (by 21 ±12 cm.s^{-1}, or 31 ±13%, P <0.01), CBVC (by 0.2 ±0.2 cm.s^{-1}mm Hg^{-1}, P <0.01) and MAP (by 10 ±10 mm Hg, P <0.01), relative to the SHAM trial. At LBNP tolerance the following variables were higher in the CO_2 trial relative to the SHAM trial: $P_{ET}CO_2$ (by 18 ±5 mm Hg, P <0.01), ventilation (by 9.1 ±12.0 L.min^{-1}, P <0.01), tidal volume (by 0.3 ±0.4 L, P =0.02) and respiratory rate (by 3 ±4 breaths per minute P =0.01). Likewise, $MCAv_{mean}$ (by 18 ±10 cm.s^{-1}, or 25 ±13%, P <0.01) and CBVC (by 0.2 ±0.2 cm.s^{-1}mm Hg^{-1}, P <0.01) were higher in the CO_2 trial at LBNP tolerance. Despite those findings, MAP and HR were not different (P >0.05) between trials at LBNP tolerance. Both trials showed a similar (P =0.82) relative bradycardia at LBNP tolerance, with HRs decreasing 23 ±12 and 24 ±19 from maximum during the final LBNP stage in the SHAM and CO_2 trials respectively.

Discussion

This is the first study to examine whether elevating cerebral perfusion via inhalation of a hypercapnic gas mixture improves LBNP tolerance under heat stress conditions. The novel findings from this study are: i) inhaling a hypercapnic gas mixture restores $MCAv_{mean}$ to pre-LBNP values, resulting in cerebral perfusion being elevated at LBNP tolerance as compared to the control trial (Figure 2), but ii) this higher cerebral perfusion did not improve LBNP tolerance.

Restoration of $MCAv_{mean}$ during hyperthermic LBNP

In the current study, inhaling a hypercapnic gas mixture restored $MCAv_{mean}$ to pre-LBNP values. Previous studies have shown that in heat-stressed individuals returning $P_{ET}CO_2$ to isocapnic values only partially restores $MCAv_{mean}$ when supine or seated (4, 11, 33). Thus, other modulators of cerebral perfusion, such as reductions in perfusion pressure or an increased sympathetic activity, seemingly contribute to heat-related reductions in $MCAv_{mean}$ (3). In the current study, heat and LBNP induced reductions in $MCAv_{mean}$ were essentially ameliorated by inhaling a 5% CO_2 gas mixture

and elevating $P_{ET}CO_2$. Similarly, clamping $P_{ET}CO_2$ during hyperthermic head-up tilt restores cerebral perfusion to hyperthermic supine values (29). Furthermore, with severe heat stress (~+1.8°C T_c) hyperventilation hypocapnia appears the primary mechanism in reducing cerebral perfusion (29). Thus, in the presence of a strong hyperventilation stimulus, such as severe hyperthermia and/or a hypotensive challenge, elevating $P_{ET}CO_2$ restores cerebral perfusion.

Cerebral perfusion, LBNP tolerance and circulatory collapse

Under normothermic conditions, hypocapnia-related cerebral hypoperfusion can be reversed by rebreathing CO_2 (30) and LBNP tolerance is improved by inhaling 5% CO_2 (18). As shown in the present data, inhaling a 5% CO_2 gas mixture during hyperthermia circumvents hyperventilatory hypocapnia and accompanying reductions in cerebral perfusion. However, this CO_2 load did not improve LBNP tolerance, which is surprising given that hypercapnia significantly elevated cerebral perfusion and CBVC. Indeed, relative to pre-LBNP, in the SHAM trial LBNP tolerance was accompanied by a 27 ±9% reduction in $MCAv_{mean}$, whereas in the CO_2 trial, LBNP tolerance was accompanied by just a 10 ±10% reduction in $MCAv_{mean}$. Despite these differences, similar decreases in MAP and HR occurred in both the CO_2 and SHAM trials, confirming that LBNP-induced circulatory collapse was achieved under both conditions. These findings indicate that inhaling 5% CO_2 dissociated cerebral perfusion from circulatory collapse during simulated hemorrhage in hyperthermic individuals, demonstrating that cerebral hypoperfusion is not requisite for cardiovascular collapse.

Cardiovascular (or circulatory) collapse occurs when cardiac output falls to critically low levels, often in concert with reduced sympathetic activity (8). This, accompanied by increases in cardiac parasympathetic activity, results in a sudden bradycardia and/or decrease in systolic blood pressure (7, 8). In the current study, there were similar decreases in MAP and HR in both the CO_2 and SHAM trial at LBNP tolerance. Thus, both trials exhibited typical hallmarks of cardiovascular collapse

(sympathoinhibition and vagal activation) that resulted in a similar reduction in MAP without a corresponding physiologically relevant reduction in $MCAv_{mean}$ in the CO_2 trial.

Interestingly, the current data indicate that cardiac vagal discharge and accompanying bradycardia that typically preceding syncope may be unrelated to cerebral perfusion under hyperthermic conditions. This is perhaps not surprising given that this bradycardia has been proposed to be mediated by reductions in ventricular volumes and subsequent activation of cardiac vagal afferents (9). Furthermore, other studies have shown a dissociation between cerebral perfusion and LBNP tolerance in normothermic individuals; that is LBNP intolerance persisted despite elevated cerebral perfusion (20), while hyperventilation-induced reductions in cerebral perfusion during LBNP failed to initiate premature presyncope or hemodynamic collapse (23). These and the present findings support the hypothesis that cerebral perfusion may not always be the primary factor leading to intolerance to a hypotensive challenge. That cerebral perfusion can essentially be maintained in the face of profound central hypovolemia could have important ramifications for trauma and hemorrhage treatment; although, it is unclear whether CO_2-induced increases in cerebral perfusion would have prolonged consciousness should the trial have continued to the point of unconsciousness. Indeed, in the current study cardiovascular measures were the primary objective criteria used to determine LBNP cessation.

Ventilation and hyperthermic LBNP

Heat stress often causes hyperventilation and related hypocapnia, evidenced in the present investigation by elevating ventilation ~3.1 $L.min^{-1}$ and decreasing $P_{ET}CO_2$ ~4 mm Hg in both the SHAM and CO_2 trials prior to LBNP. This heat-induced hyperventilation is similar (13) or lower (6, 12) than that reported in other studies. As anticipated (5, 31), ventilation continued to increase and $P_{ET}CO_2$ to decrease with progressive LBNP in the SHAM trial.

Hypercapnia caused further increases in ventilation in the CO_2 trial relative to that which occurred with the SHAM trial. Similar hypercapnic ventilatory responses

have been shown during normothermic LBNP (40 mm Hg) (22). Such increases in ventilation, and particularly tidal volume, may aid venous return and subsequently help maintain cardiac output via the respiratory pump (2, 36), though it is unknown whether this occurs during hyperthermia. Certainly, the maintenance of MAP during severe LBNP in the CO_2 trial, versus the gradual reduction in MAP during the SHAM trial, suggests that larger increase in ventilation during the CO_2 trial augments venous return. However, despite this, hypercapnia did not improve LBNP tolerance under heat stress conditions, thereby indicating that any increases in cardiac output due to increased tidal volume was insufficient to improve tolerance.

Technological considerations

Transcranial Doppler was used to measure blood velocity in the middle cerebral artery. This approach has been used as an index of cerebral blood flow, as this artery supplies ~80% of the blood flow received by each cerebral hemisphere (24) and its diameter is reported to not change during moderate CO_2 and blood pressure perturbations (15, 35). However, recent studies have shown that the regulation of blood flow differs between the brainstem and cortex with the brainstem being less sensitive to hypocapnia (34, 39). Although speculative, it may be that hypercapnia-induced increases in $MCAv_{mean}$ during hyperthermic LBNP do not reflect comparable increases in blood flow to other areas of the brain, namely the brainstem. It is also important to consider potential differences in cerebral hemodynamics during an LBNP challenge versus the upright posture. Orthostatic-induced syncope is reported to occur upon an ~50% reduction in $MCAv_{mean}$ (38). However, the current study indicates that presyncopal symptoms can occur without a meaningful reduction in $MCAv_{mean}$ during LBNP.

Implications

The current study demonstrates that the administration of 5% CO_2 could be advantageous in the maintenance of cerebral perfusion during a hypotensive challenge, attenuating the reduction in cerebral perfusion even at circulatory collapse. These

findings could have implications for the treatment of individuals suffering from a hemorrhagic injury, when maintenance of brain perfusion becomes paramount. Though, it should be noted that the tracking of the $MCAv_{mean}$ will not necessarily enable the prediction or identification of circulatory collapse or shock, at least in heat stressed individuals.

Conclusions

During hyperthermia, inhaling a hypercapnic gas mixture and circumventing hyperventilation-induced hypocapnia does not improve LBNP tolerance, despite restoring cerebral perfusion. This disassociation between cerebral perfusion and systemic circulatory responses during central hypovolemia indicates that cerebral perfusion may be maintained in the face of a severe hypotensive challenge, even to the point of circulatory collapse.

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Table 1: Baseline thermal, hemodynamic and respiratory measures during normothermia and heat stress (immediately prior to lower body negative pressure, Pre-LBNP) for both the control (SHAM) and CO_2 trials.

	Normothermia		Heat stress (Pre-LBNP)	
	Baseline SHAM	Baseline CO_2	Baseline SHAM	Baseline CO_2
T_c (°C)	36.8 ±0.3	36.7 ±0.3	38.1 ±0.3 **#**	38.0 ±0.2 **#**
Tsk (°C)	34.5 ±0.3	34.4 ±0.5	38.4 ±0.5 **#**	38.3 ±0.6 **#**
$MCAv_{mean}$ ($cm \cdot s^{-1}$)	65 ±17	66 ±12	55 ±15 **#**	57 ±14 **#**
CBVC ($cm \cdot s^{-1}$ mm Hg^{-1})	0.8 ±0.2	0.8 ±0.2	0.7 ±0.2	0.7 ±0.2
$P_{ET}CO_2$ (mm Hg)	41 ±3	41 ±3	36 ±5 **#**	38 ±3 **#**
Ventilation BTPS ($L.min^{-1}$)	8.1 ±2.2	8.0 ±3.7	11.0 ±3.8 **#**	9.9 ±4.3 **#**
Tidal volume (L)	0.6 ±0.2	0.6 ±0.2	0.9 ±0.4 **#**	0.9 ±0.4 **#**
Respiratory rate	14 ±2	14 ±4	15 ±5	13 ±5
MAP (mm Hg)	86 ±10	83 ±10	80 ±7	79 ±6
HR (bpm)	57 ±8	58 ±8	96 ±14 **#**	95 ±12 #

T_c , body core temperature; Tsk, mean skin temperature; $MCAv_{mean}$, middle cerebral artery velocity; CBVC, cerebrovascular conductance; $PETCO_2$, end-tidal carbon dioxide; MAP, mean arterial pressure; HR, heart rate. **#** Significantly different from normothermic baseline, $P < 0.05$.

Figure 1: Ventilatory measures (BTPS) during both heat stress lower body negative pressure (LBNP) tests where subjects inhaled either a hypercapnic gas mixture or room air (SHAM). $P_{ET}CO_2$: end-tidal partial pressure of carbon dioxide. ‡ Significantly different from SHAM trial (P <0.05); [1] Significantly different from 0 mm Hg (P <0.05); [2] Significantly different from 20 mm Hg (P <0.05); [3] Significantly different from severe LBNP (P <0.05).

Figure 2: Cerebrovascular measures during both heat stress lower body negative pressure (LBNP) tests where subjects inhaled either a hypercapnic gas mixture or room air (SHAM). $MCAv_{mean}$: mean middle cerebral artery blood velocity; CBVC: cerebrovascular conductance. ‡ Significantly different from SHAM trial (P <0.05); [1] Significantly different from 0 mm Hg (P <0.05); [2] Significantly different from 20 mm Hg (P <0.05).

Figure 3: Mean arterial pressure (MAP) and heart rate (HR) measures during both heat stress lower body negative pressure (LBNP) tests where subjects inhaled either a hypercapnic gas mixture or room air (SHAM). ‡ Significantly different from SHAM trial (P <0.05); [1] Significantly different from 0 mm Hg (P <0.05); [2] Significantly different from 20 mm Hg (P <0.05); [3] Significantly different from severe LBNP (P <0.05).

Figure 1.

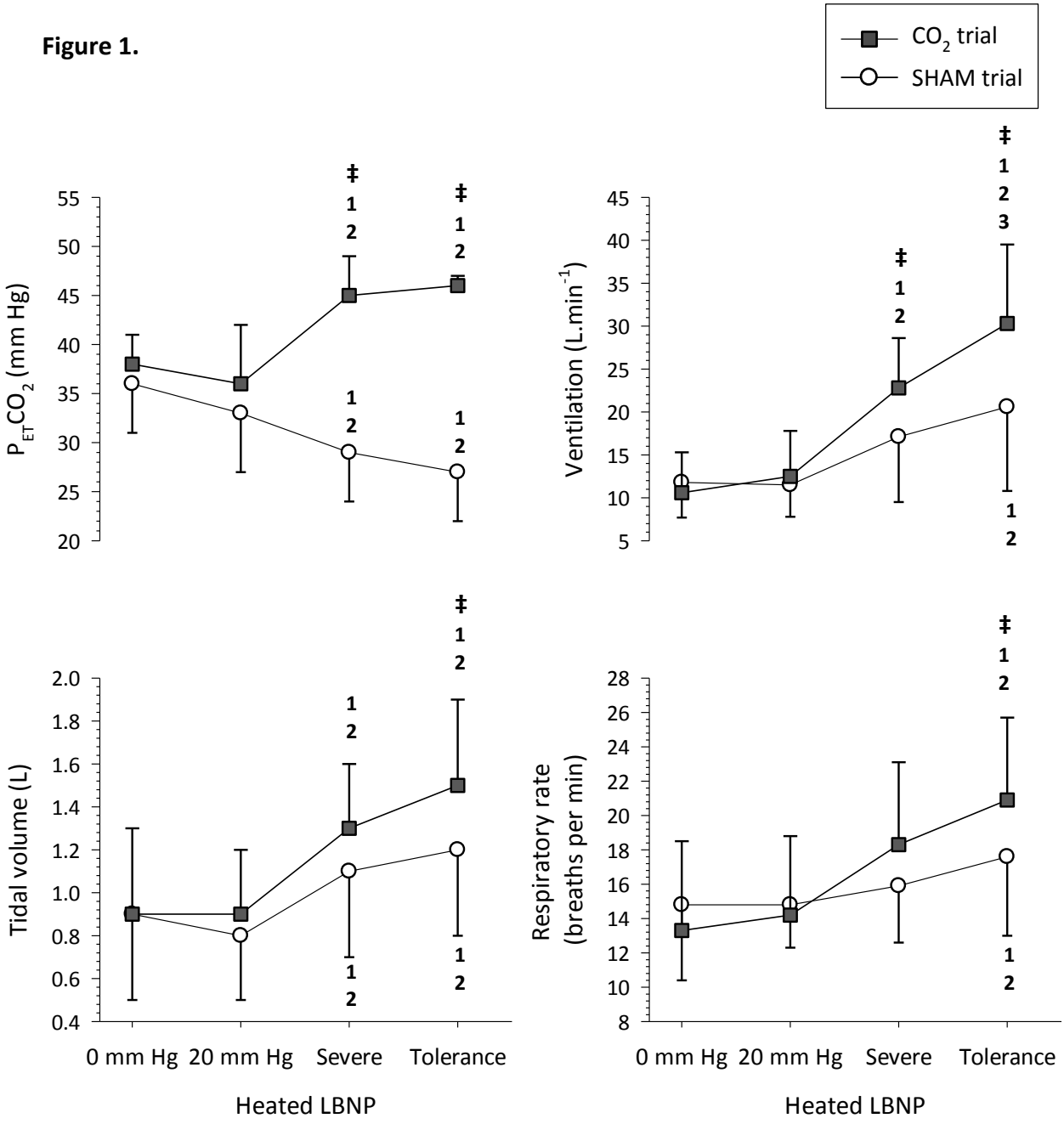

CO2 trial
SHAM trial
PETCO2 (mm Hg)
Ventilation (L.min-1)
Tidal volume (L)
Respiratory rate (breaths per min)
0 mm Hg
20 mm Hg
Severe
Tolerance
Heated LBNP

Figure 2.

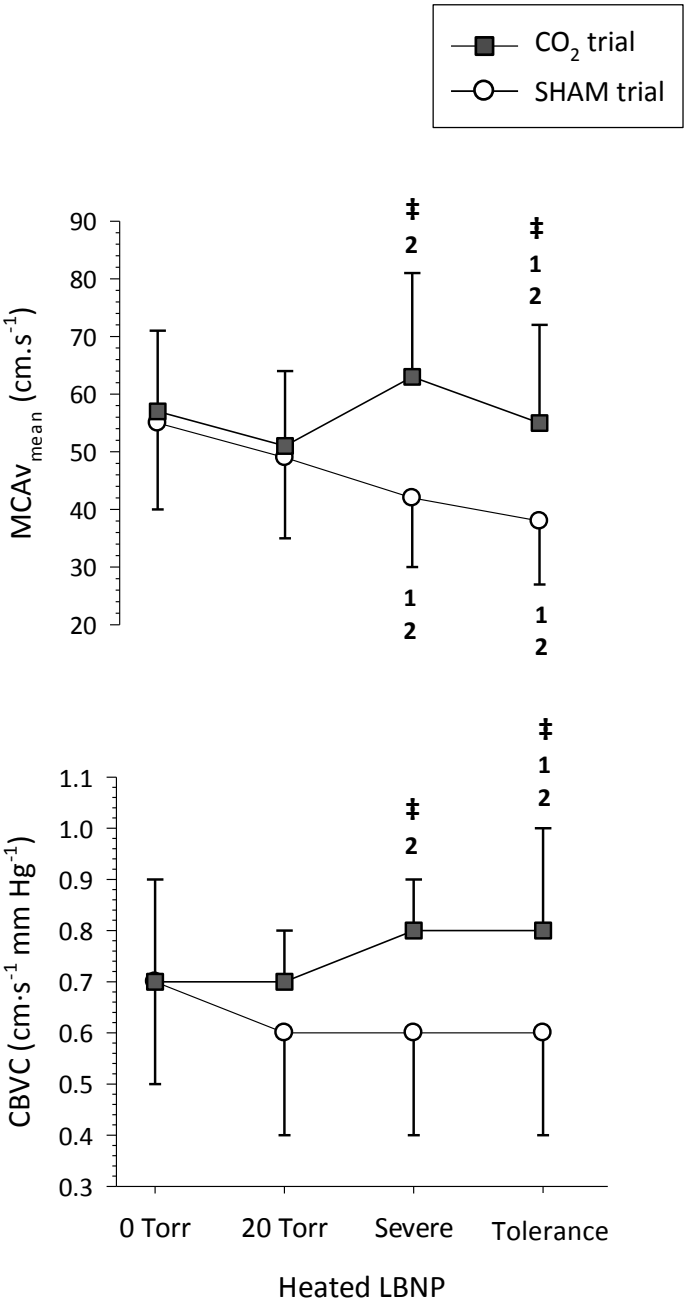
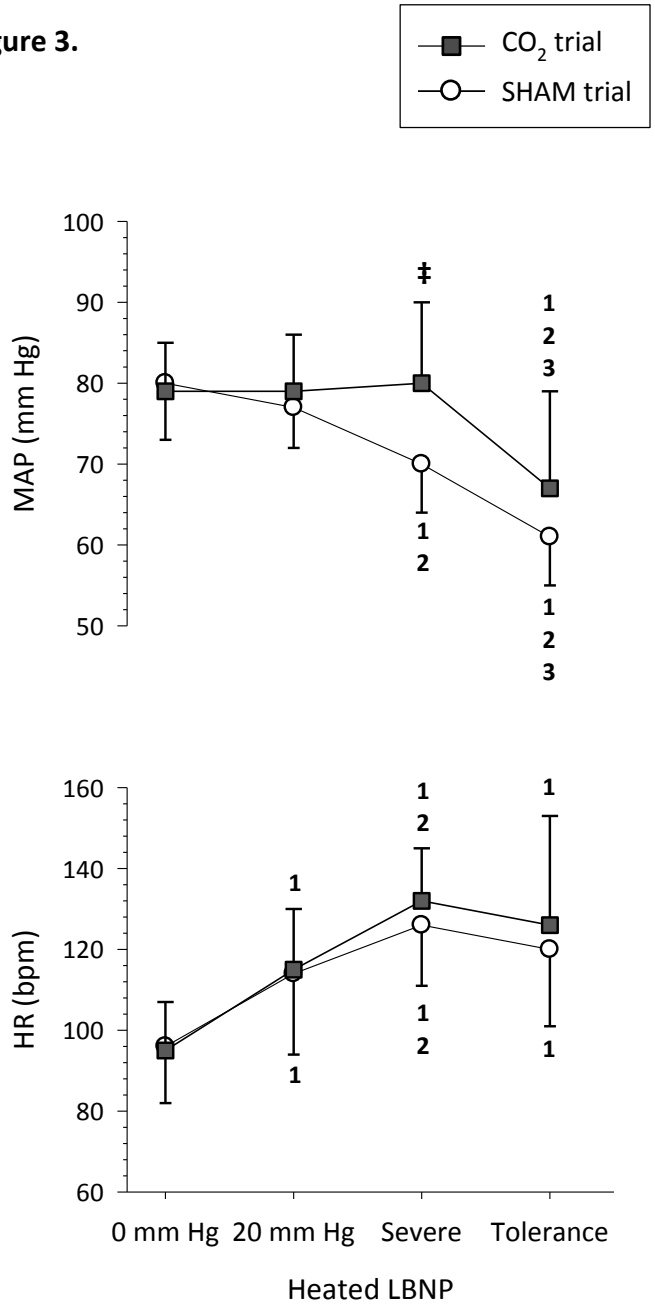

CO2 trial
SHAM trial
MCAvmean (cm.s-1)
90
80
70
60
50
40
30
20
‡ 2
‡ 1 2
1 2
1 2
CBVC (cm·s-1 mm Hg-1)
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
‡ 2
‡ 1 2
0 Torr
20 Torr
Severe
Tolerance
Heated LBNP

Figure 3.


CO2 trial
SHAM trial
MAP (mm Hg)
100
90
80
70
60
50
‡
1
2
3
1
2
1
2
3
HR (bpm)
160
140
120
100
80
60
1
2
1
1
2
1
1
0 mm Hg
20 mm Hg
Severe
Tolerance
Heated LBNP